

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 5 -

REMARKS

Claims 1-19 are pending in the application. Claim 1 has been amended to conform the claim to proper claim format. No new matter has been added by virtue of this amendment and entry is respectfully requested.

Attached hereto, are the 37 C.F.R. § 1.1.32 Declaration (as "Exhibit A") of Dr. Ohl, an expert in the field, providing an assessment of the cited references and the instant invention. Consideration and entry is respectfully requested.

Claim Rejections Under 35 U.S.C.§ 112

Claim 7 is rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the .

Applicants respectfully traverse.

Applicants describe in detail what a biological fluid comprises in the female subject. For example, on page 7, lines 14-21 through to page 8, lines 1-5:

The biological sample containing sperm can vary according to the site selected for contacting the sperm with the agent. In some embodiments, the fluid component of the sample is that of the ejaculate, i.e., the seminal plasma. As an example, a semen sample may obtained from the subject and contacted with an agent in vitro. In other aspects, e.g., if the inhibition of the cytokine is performed within the reproductive tract of the male subject, the fluid can be that fluid produced by one or more of the tissues lining the male reproductive tract, including the seminiferous tubules, epididymis, vas deferens, prostate, seminal vesicles and urethra. In yet other embodiments, it is envisioned that the agent may be contacted with sperm that have been deposited in the female reproductive tract. In that case, the fluid can include any fluid produced by any tissue of the female reproductive tract, including fluid produced by any of the ovaries,

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 6 -

fallopian tubes, uterus, cervix or vagina. The fluid in the female reproductive tract can also be deposited semen, or an admixture of semen and any other fluid present in the female reproductive tract.

Thus one of ordinary skill in the art would know the “metes and bounds” of the instant claim. As the above passage states, the biological fluid is any fluid from a female reproductive tract and can include deposited semen. Applicants submit that claim 7 is clear on its face.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 102

Claims 1, 2, 5, 6, 8-19 are rejected under 35 U.S.C. § 102(b) as being anticipated by Alexander et al (US 6,180,355 B1).

Applicants respectfully traverse.

Applicants invention is directed, in part, to method of increasing motility of sperm, by providing from a subject a biological sample comprising sperm and at least one cytokine; and contacting the biological sample with an agent that inactivates or reduces the biological activity of the at least one cytokine selected from the group consisting of TNF α , IL1 β , and IL6.

Alexander et al., neither teaches nor discloses methods of increasing sperm motility. Alexander et al., discusses diagnosing of CPPS and does not teach treating infertility by contacting a semen sample that contains cytokines with an agent that inactivates or reduces the activity of the cytokines. The Examiner asserts that Alexander et al., anticipates the instant invention, asserting that :

Alexander teaches the use of sandwich ELISA for cytokines in a semen sample (column 11 line 5). The use of antibodies that specifically bind to

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 7 -

the cytokines in the semen such as TNF α , IL1 β , and IL6 is taught (column 11 line 10) (claims 1,5,6,8-15). The subject's condition causes increased cytokine levels in the semen, which inherently impairs fertility (as taught by Applicant page 5 lines 1-5).

Since Alexander is explicitly practicing all the steps of Applicant's method as claimed by administering cytokine antibodies that specifically bind to the claimed cytokines in a semen sample, Alexander anticipates Applicant's claimed method.

The Examiner's allegations that the use of an ELISA for detection of cytokines in a semen sample and the binding of antibodies to cytokines in the semen, does not teach each and every claim limitation of the instant invention. Detection of binding of antibodies to a highly diluted semen sample does not anticipate the instant invention. Furthermore, detection does not imply that Alexander *et al* increases sperm motility. Detection versus treating are separate entities. Antibody types, and concentrations etc useful in increasing sperm motility is not the same as detecting in an ELISA. In addition, the Examiner assertions that Applicants teach an inherency (see, office action, page 3, 6th paragraph), is incorrect.

Alexander does not discuss or teach administration of anti-cytokine antibodies or agents to increase sperm motility. Furthermore, treatment of sexual dysfunction by administering anti-TNF α antibodies to a patient suffering from CPPS has no bearing on treating fertility, i.e. sexual function vs. fertility. Alexander et al., neither teaches nor discloses treatment of actual semen samples with any anti-cytokine agents. In contrast, Alexander et al., discusses systemic administration of an anti-TNF- α antibody.

Alexander discusses using generally available techniques of analysis of cytokines to diagnose and treat "Chronic Pelvic Pain Syndrome (CPPS)" or non-bacterial prostatitis. Alexander makes further reference to the symptoms and side effects of CPPS including sexual dysfunction. Alexander makes no reference to infertility, nor is it alleged in Alexander's patent or in the general medical literature that infertility is caused by CPPS. Further, it is common

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 8 -

knowledge in the general medicine that infertility and sexual dysfunction are separate entities which should not be confused.

In summary, Alexander discusses cytokines in the semen to diagnose a condition or disease such as CPPS/Chronic Prostatitis. Alexander does not demonstrate or suggest that the administration of the anticytokine agents/antibodies are active in the seminal plasma or bind to the cytokines there. In fact, one of ordinary skill in the art would recognize that they are by example and by intent treating a systemic disease (supposedly autoimmune) which has seminal cytokines as its markers.

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim Rejections Under 35 U.S.C. § 103

Claims 1, 2, 5, 6, 8-19 were rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1) in view of Gruschwitz et al (*Journal of Andrology* 1996) and Angelopoulos et al (*Fertility and Sterility* 1999).

Applicants respectfully traverse.

Alexander has been discussed above. The significance and role of elevated cytokines in Alexander's invention is directed to markers of a completely different disease. Alexander et al., neither teach or disclose treating the seminal plasma is helpful in treating any disease. In contrast, the instant invention teaches, in part, that elevated cytokines in the seminal plasma cause reduced sperm motility which can be treated in a novel manner, i.e., by neutralizing these cytokines in the seminal plasma. Combining Gruschwitz with Alexander does not result in the instant invention. Gruschwitz discusses a myriad of conflicting data and is directed to urogenital infections which would result in an inflammatory immune response. Applicants, in contrast,

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 9 -

have demonstrated causation in that treating seminal plasma *in vitro* with anticytokine agents improves sperm motility in patients with SCI. Further, the instant research has shown no evidence of chronic prostatitis in SCI men, the very subjects from which the semen samples were obtained (Randall et al., *J Urol* 2003;170:897-900). Angelopoulos et al, does not cure the deficiencies of Alexander in view of Gruschwitz. Angelopoulos reported the effects of tissue culture versus addition of pentoxifylline and 2-deoxyadenosine on non-motile sperm in testicular biopsies of azoospermic men. They did not study cytokines or seminal plasma or anticytokine agents. Angelopoulos further is directed to the occurrence of immotile testicular spermatozoa in testicular biopsies as a physiological event resulting from immaturity or attachment to Sertoli cells – not a pathologic condition.

Applicants further provide the declaration of an expert, Dr. D. Ohl, under 37 C.F.R. § 1.132, wherein, Dr. Ohl describes, as one of ordinary skill in the art that these references do not rise to the level of obviousness.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 3 and 4 are rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1), Gruschwitz et al (*Journal of Andrology* 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Basu et al (*Journal of Andrology* 2002).

Applicants respectfully traverse.

Alexander in view of Gruschwitz and Angelopoulos were discussed above. Applicants submit that the declaration filed by inventor Basu on September 13, 2006 states that the instant

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 10 -

invention was conceived prior to the publication by Basu. In paragraph 7 of the Declaration, inventor Basu states the following:

Some of the Examiner's objections are based on publications by Basu. The Examiner believes that these Basu publications preceded the patent application. Basu is one of our co-inventors. It is my understanding that the invention disclosure date is the key date. The invention disclosure was submitted to the University of Miami on July 31, 2002. The date of conception as listed on the Invention Disclosure form was Jan. 12, 2001. The examiner asserts that "one of ordinary skill in the art would have been motivated to use the method of Alexander because Alexander teaches that the method can be used to treat conditions associated with elevated levels of a cytokine....."

Once again, we assert that the method referred to treats conditions such as CPPS by administration of anti cytokine agents orally or parenterally. Our method treats an unrelated condition, low sperm motility, by the addition anti cytokine agents to the seminal plasma in vitro (see above).

As such, Applicants submit that the instant invention pre-dates the cited reference. There is no motivation to combine Alexander et al., with Basu et al., as each discuss different conditions and diagnosis of CPPS as discussed by Alexander would not result in a method of treatment infertility as taught by the instant invention. Further, as stated by the inventors in the 37 C.F.R. Rule 1.132 Declaration, Basu is a co-inventor and the conception of the instant application preceded the Basu publication. As such, Basu et al is not a proper reference.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claims 3 and 4 were rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B1), Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Brackett et al (Physical Therapy 1996).

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 11 -

Applicants respectfully traverse.

As discussed above, Alexander discusses a method of treatment by systemically administering agents to the patient directly to treat CPPS. Administration is via oral or various injectable routes. Since the invention deals with CPPS, and Non Bacterial Prostatitis, no teaching or disclosure is made for the direct treatment of the seminal plasma since anyone with skill in the art would recognize that manipulation of the components of the seminal plasma would not and does not affect a prostatic disorder. Furthermore, Alexander would discourage and teach away from the direct treatment of the seminal plasma as taught by Applicants.

Alexander discusses diagnosing of a disease. Further, they aim to treat the disease state (not the cytokines in the seminal plasma) by giving the patient anticytokine agents. In contrast, Applicants treat the seminal plasma and sperm after identifying these cytokines is a novel way of improving sperm motility. Alexander does not teach or disclose elevated cytokines in the seminal plasma causing reduced sperm motility and treatment of the seminal plasma.

As discussed above, Alexander, in view of Gruschwitz, and Angelopoulos are centered around the interpretation of treating a condition “associated with” as discussed by Alexander. Applicants submit that one of ordinary skill in the art would realize that this “condition” means systemic illness such as CPPS (or even rheumatoid arthritis) that is indicated or marked by elevated cytokines in the seminal plasma rather than the treatment of the effects of cytokines in the seminal plasma on sperm motility. Brackett *et al.*, does not teach or disclose that sperm may be treated with anticytokine agents to increase sperm motility. Substituting Brackett for Alexander’s systemic treatment of a disease is not an obvious leap to make for one of ordinary skill in the art. For example, Alexander would teach away from directly treating the seminal plasma. There is no teaching as to the amounts, types of antibodies, that motility would be affected etc.

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 12 -

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

Claim 7 is rejected under 35 U.S.C. 103(a) as being unpatentable over Alexander et al (US 6,180,355 B), Gruschwitz et al (Journal of Andrology 1996) and Angelopoulos et al (Fertility and Sterility 1999) as applied to claims 1, 2, 5, 6, and 8-19 above, and further in view of Gerris (European Society of Human Reproduction and Embryology 1999).

Applicants respectfully traverse.

Alexander, in view of Gruschwitz, and Angelopoulos was discussed above and for the sake of brevity the arguments will not be repeated here as they are applicable to this rejection. Gerris et al., does not cure the deficiencies of Alexander, in view of Gruschwitz, and Angelopoulos. Gerris discusses that sperm from the vagina can be retrieved from ICSI. No therapeutic or diagnostic techniques are ascribed to these sperm. As such, Applicants submit that Alexander, in view of Gruschwitz, Angelopoulos and Gerris neither teach or disclose the instant invention.

In view thereof, Applicants respectfully request reconsideration and withdrawal of the instant rejection.

CONCLUSION

Applicants respectfully request entry of the foregoing remarks and reconsideration and withdrawal of all rejections. It is respectfully submitted that this application with claims 1-19 define patentable subject matter and is in condition for allowance. Accordingly, Applicant respectfully requests allowance of these claims.

In re Application of: Brackett N. L., et al.
Confirmation No: 6890
Application No.: 10/748,637
Examiner: SCHUBERG, L. J.
Response to November 29, 2006 Office Action
Page- 13 -

This response is being timely filed with a petition for a one month retroactive extension of time and the required fees. Although, Applicants believe that no further extensions of time are required with submission of this paper, Applicants request that this submission also be considered as a petition for any further extensions of time if necessary. The Commissioner for Patents and Trademarks is hereby authorized to charge the amount due for any retroactive extensions of time and any deficiency in any fees due with the filing of this paper or credit any overpayment in any fees paid on the filing or during prosecution of this application to Deposit Account No. 50-0951.

Respectfully submitted,
AKERMAN SENTERFITT

Date: March 29, 2007



Nicholas A. Zachariades, Ph.D.
Reg. No. 56,712
AKERMAN SENTERFITT
P.O. Box 3188
West Palm Beach, FL 33402-3188
Tel: 561-653-5000

Docket No. 7230-9